PATENT SPECIFICATION 842,325

NO DRAWINGS.

Inventors :—STANLEY BIRTWELL, WILLIAM GLYNNE MOSS JONES and ROY FREDERICK MAISEY.

Date of filing Complete Specification : Sept. 17, 1957.

Application Date : Oct. 1, 1956. No. 29840/56.

Complete Specification Published : July 27, 1960.

Index at Acceptance:—
Class 81(1), B1(B3 : C : D : H : L : N : P : R1 : S : T), B2(B3 : C : D : H : L : N : P : R1 : S : T).

International Classification :—A61k.

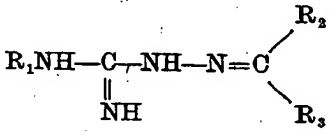
COMPLETE SPECIFICATION.

Pharmaceutical Compositions containing Aminoguanidine Derivatives.

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :—

This invention relates to new pharmaceutical compositions and more particularly it relates to new pharmaceutical compositions containing guanidine derivatives which possess therapeutic properties especially in the treatment of allergic and inflammatory conditions.

According to the invention we provide new pharmaceutical compositions wherein the active ingredient is at least one guanidine compound of the formula :—



wherein R_1 stands for an aryl radical which may optionally be substituted, R_2 stands for hydrogen or for a hydrocarbon radical which may optionally be substituted and R_3 stands for a hydrocarbon radical or for a heterocyclic radical both of which may optionally be substituted, provided that when R_3 stands for a heterocyclic radical R_2 stands for hydrogen, and wherein R_2 and R_3 may be joined, together with the adjacent carbon atom, to form a homocyclic or heterocyclic ring, or a salt thereof.

As suitable salts of the said guanidine compounds there may be mentioned for example mineral acid salts for example the hydrochlorides and organic acid salts for example the acetates and salicylates.

As suitable compounds of the above stated formula there may be mentioned for example those compounds which are described in our co-pending Applications Nos. 29837/56, 29838/56 and 29839/56 (Serial Nos. 842,322, 842,323 and 842,324) for example N^1-5 : 6 : 7 : 8-tetrahydro-2-naphthyl-N^2-isobutylideneaminoguanidine, N^1-4-methylphenyl-N^2-3′-indolylmethyleneaminoguanidine, N^1-4-methylphenyl-N^2-2′-thienylmethyleneaminoguanidine, N^1-4-methylphenyl-N^2-*p*-dimethylaminocinnamylideneaminoguanidine, N^1-4-methylphenyl-N^2-3′-hydroxybutylideneaminoguanidine, N^1-2 : 4-dimethylphenyl-N^2-ethylideneaminoguanidine, N^1-4-chlorophenyl-N^2-4′-azabenzylideneaminoguanidine, N^1-4-acetamidophenyl-N^2-1′-methylbutylideneaminoguanidine, N^1-2 : 4-dimethylphenyl-N^2-*sec*-butylideneaminoguanidine, N^1-4-methylphenyl-N^2-*iso*propylideneaminoguanidine, N^1-5 : 6 : 7 : 8-tetrahydro-2-naphthyl-N^2-*cyclo*hexylideneaminoguanidine, N^1-2 : 3-dimethylphenyl-N^2-1′-methyl-4′-diethylaminobutylideneaminoguanidine, N^1-5 : 6 : 7 : 8-tetrahydro-2-naphthyl-N^2-*sec*-butylideneaminoguanidine, N^1-3 : 4-dimethylphenyl-N^2-*iso*propylideneaminoguanidine, N^1-4-chlorophenyl-N^2-*trans*-2′-decalylideneaminoguanidine, N^1-2 : 4 : 5-trimethylphenyl-N^2-*cyclo*hexylideneaminoguanidine, N^1-4-ethylphenyl-N^2-*iso*propylideneaminoguanidine, N^1-2 : 4-di-

chlorophenyl - N^2 - *cyclo*hexylideneaminoguanidine, N^1 - 4 - dimethylaminophenyl-N^2 - 1' - methylbutylideneaminoguanidine methiodide, N^1 - 4 - methylsulphonylphenyl-N^2 - 1' - methylbutylideneaminoguanidine, N^1 - 4 - fluorophenyl - N^2 - *iso*propylideneaminoguanidine, N^1 - 4 - dimethylaminophenyl - N^2 - *iso*propylideneaminoguanidine, N^1 - 4 - bromophenyl - N^2 - *iso*propylideneaminoguanidine, N^1 - phenyl - N^2 - 1'-methyl - 4' - diethylaminobutylideneaminoguanidine, N^1 - phenyl - N^2 - benzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl-N^2 - benzylideneaminoguanidine, N^1 - 2 : 4-dimethylphenyl - N^2 - α - methylbenzylideneaminoguanidine, N^1 - phenyl - N^2 - 4 - dimethylaminobenzylideneaminoguanidine, N^1-3 - methylphenyl - N^2 - 4' - acetamidobenzylideneaminoguanidine, N^1 - 3 : 4 - dimethylphenyl - N^2 - 4' - dimethylaminobenzylideneaminoguanidine, N^1 - 4 - methylphenyl - N^2-4' - dimethylaminobenzylideneaminoguanidine, N^1 - 4 - methylphenyl - N^2 - 3' : 4'-methylenedioxybenzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 4' - methoxybenzylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - 3' : 4' - methylenedioxybenzylideneaminoguanidine, N^1 - 4 - methoxyphenyl - N^2 - 4' - dimethylaminobenzylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2-4' - acetamidobenzylideneaminoguanidine, N^1 - 5 : 6 : 7 : 8 - tetrahydro - 2 - naphthyl-N^2 - 4' - dimethylaminobenzylideneaminoguanidine, N^1 - 3 - methyl - 4 - chlorophenyl-N^2 - 4' - dimethylaminobenzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2-4' - nitrobenzylideneaminoguanidine, N^1 - 4-methylthiophenyl - N^2 - 3' - hydroxybenzylideneaminoguanidine and N^1 - 4 - acetamidophenyl - N^2 - 4' - dimethylaminobenzylideneaminoguanidine.

The pharmaceutical compositions with which this invention is concerned may be in the form of compositions suitable for oral use, compositions suitable for topical application or compositions suitable for injection purposes.

Suitable oral compositions may be for example in the form of tablets, coated or uncoated, aqueous or oily suspensions, dispersible granules, emulsions or hard or soft capsules.

The said tablets contain the active ingredient in admixture with pharmaceutical excipients known to be suitable in the manufacture of tablets. Suitable pharmaceutical excipients may be for example calcium carbonate or calcium phosphate, granulating and disintegrating agents for example maize starch and lubricating agents for example magnesium stearate. The tablets may be uncoated or they may be coated by known techniques to delay disintegration in the presence of gastric juice and thereby provide a sustained action over a longer period.

The said tablet compositions may be formulated so that for every 100 parts by weight of the composition there is present between about 25 parts by weight and about 95 parts by weight of the appropriate guanidine compound or a salt thereof and preferably between about 50 parts and about 90 parts by weight of the said guanidine compound or a salt thereof.

The said aqueous suspensions may be formulated from suitable sparingly-soluble salts of the guanidine compounds for example N^2 - *iso*propylideneamino - N^1 - *p* - tolylguanidine, salicylate in a sweetened aqueous medium for example aqueous sucrose solution containing a suspending agent for example sodium carboxymethylcellulose, sodium alginate or polyvinyl pyrrolidone and a dispersing agent. Suitable dispersing agents may be a naturally occurring phosphatide for example lecithin or condensation products of ethylene oxide with fatty acids for example polyoxyethylene stearate or fatty alcohols for example heptadeca-ethyleneoxycetanol, or with partial esters derived from the common fatty acids and a hexitol for example polyoxyethylene sorbitol mono-oleate, or with partial esters derived from the common fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan mono-oleate. The suspensions so obtained may contain suitable preservatives and desirably also a flavouring agent.

The dispersible granules for oral use contain the active ingredient admixed with a dispersing agent and a suspending agent in the presence of suitable preservatives. Suitable dispersing and suspending agents are those mentioned above. Auxiliary excipients for example sweetening agents for example sucrose and flavouring and colouring agents may be present.

Oily suspensions for oral use may be formulated by suspending the active ingredient in a suitable vegetable oil, for example arachis oil, sesame oil or coconut oil in the presence of a thickening agent for example beeswax. Sweetening agents for example icing sugar and saccharin sodium and flavouring agents for example caramel may be added to provide a palatable oral preparation.

The pharmaceutical compositions, as indicated above, may also be in the form of emulsions suitable for oral use. The said emulsions are preferably oil-in-water type emulsions which preferably contain the active ingredient in the form of a suitable salt for example the oleate dissolved in the oil phase. Suitable emulsifying agents may be naturally-occurring gums for example gum acacia or gum tragacanth, naturally-occurring phosphatides for example soya bean lecithin and esters or partial esters derived from the common fatty acids for example lauric,

palmitic, stearic and oleic acid and hexitol anhydrides for example sorbitan mono-oleate and the corresponding condensation products of the said partial esters with ethylene oxide for example polyoxyethylene sorbitan mono-oleate. The aqueous phase may contain a sweetening agent for example a polyhydric alcohol for example glycerol or sorbitol and a suitable oily base may be for example a vegetable base for example arachis oil.

Capsule formulations for oral use may for example be presented as hard gelatine capsules wherein the active ingredient is admixed with an inert solid diluent for example calcium carbonate or as soft gelatine capsules wherein the active ingredient, in the form of a suitable salt for example the oleate, is dissolved in an oily medium for example arachis oil.

The pharmaceutical compositions may furthermore be in the form of creams, ointments or pastes for topical use wherein the active ingredient is admixed with pharmaceutical excipients known to be suitable in the manufacture of such creams, ointments or pastes. The said creams are in the form of oil-in-water or water-in-oil emulsions in which the active ingredient is preferably in suspension or dissolved in the oil phase. Suitable pharmaceutical excipients may be for example suitable mixtures of oily or fatty bases for example petroleum hydrocarbons for example liquid paraffin, vegetable fats for example arachis oil, long chain aliphatic alcohols or acids for example cetyl alcohol or stearic acid, emulsifying agents for example condensation products of ethylene oxide with long chain aliphatic alcohols for example heptadeca-ethyleneoxycetanol and humectants for example polyhydric alcohols for example glycerol. Such cream compositions may be formulated so that for every 100 parts by weight of the composition there is present between 0.1 part by weight and 10 parts by weight of the appropriate guanidine compound or a salt thereof and preferably between 1 part and 3 parts by weight of the said guanidine compound or a salt thereof. The said ointments or pastes are such that the active ingredient or ingredients are dissolved in or dispersed in an anhydrous fatty base for example animal or vegetable fats or a paraffin base. The creams, ointments or pastes may also optionally contain a suitable preservative and/or a suitable anti-oxidant.

As stated above, the pharmaceutical compositions may also be in a form suitable for injection. Such injectable compositions may be for example sterile aqueous or oil suspensions, sterile powders for the preparation of injectable solutions and sterile dispersible powders for the preparation of injectable aqueous suspensions.

Compositions in the form of water-dispersible powders to which may be added an aqueous medium to provide aqueous suspensions suitable for parenteral use may be formulated from appropriate sparingly soluble salts for example N^2-*iso*propylideneamino-N^1-*p*-tolylguanidine salicylate in the presence of parenterally-acceptable suspending agents and dispersing agents. Suitable suspending agents may be for example sodium carboxymethylcellulose, sodium alginate or polyvinyl pyrrolidone. Suitable dispersing agents may be naturally-occurring phosphatides for example soya bean lecithin or condensation products of ethylene oxide with fatty acids for example polyoxyethylene stearate or fatty alcohols for example heptadeca-ethyleneoxycetanol, or with partial esters derived from the common fatty acids and a hexitol for example polyoxyethylene sorbitol mono-oleate, or with partial esters derived from the common fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan mono-oleate. Preserving agents such as methyl and propyl-*p*-hydroxybenzoate may be incorporated in such dispersible powders.

Aqueous suspensions for parenteral use may be formulated directly by dispersing an appropriate sparingly-soluble guanidine salt for example N^2-*iso*-propylideneamino-N^1-*p*-tolylguanidine salicylate in a sterile aqueous medium containing a suitable dispersing agent and suspending agent. Thus suspending agents may be sodium carboxymethylcellulose, sodium alginate or polyvinyl pyrrolidone and dispersing agents may be naturally-occurring phosphatides for example soya bean lecithin or the ethylene oxide condensation products described above for use in the formulation of sterile dispersible powders.

Injectable compositions in the form of suspensions in oily media may be prepared by dispersing the active ingredient in a suitable oily medium for example a vegetable oil for example arachis oil. Such suspensions may optionally contain a gelling agent for example aluminium stearate to delay absorption and prolong the action of the active material.

Sterile powders for use in the preparation of injectable solutions may be formulated from an appropriate water-soluble salt for example a hydrochloride for example N^1-*p*-chlorophenyl - N^2 - pent - 2 - ylideneamino-guanidine hydrochloride. Such powders preferably contain a bacteriostatic agent for example a long chain quaternary salt for example cetyl trimethylammonium chloride, to enable the use of the powders in multi-dose containers, and also inorganic salts for example sodium chloride to provide aqueous solutions isotonic with normal saline.

As stated above, the pharmaceutical compositions of this invention have useful therapeutic properties especially in the treatment of allergic and inflammatory conditions, for

example asthma, hay fever and allergic eczemas and purpuras.

The invention is illustrated but not limited by the following examples in which the parts are by weight :—

EXAMPLE 1.

250 Parts of N^2-4-dimethylaminobenzylidene - amino - N^1 - phenylguanidine are mixed with 47 parts of maize starch and the resulting mixture is compressed into slugs. The slugs are then broken down into granules by passage through a 16 mesh screen and then mixed with 3 parts of magnesium stearate. The mixture thus obtained is finally compressed into tablets which are suitable for oral use for therapeutic purposes.

EXAMPLE 2.

A mixture of 250 parts of N^2-*cyclo*hexylidene - amino - N^1 - 2 : 4 - dimethylphenylguanidine, 25 parts of maize starch and 22 parts of calcium phosphate is granulated by admixture with a sufficient quantity of methanol. The granules are sieved through a 16 mesh screen, dried at 50° C. and then mixed with 3 parts of magnesium stearate. The mixture is finally compressed into tablets which are suitable for oral administration for therapeutic purposes.

EXAMPLE 3.

The tablets prepared by either of the processes described in Examples 1 and 2 can be provided with an enteric coating by adopting conventional procedures. The tablets are tumbled in a tablet-coating pan and a sufficient quantity of a solution of 1 part of cetyl alcohol, 1 part of stearic acid, 2 parts of shellac and 6 parts of ethyl alcohol is added. When a suitable consistency has been attained, the tablets are dusted by the addition of the required amount of a mixture of 1 part of talc and 1 part of stearic acid. The procedure is repeated until tablets giving the appropriate disintegration time in artificial gastric and intestinal juices are obtained. The enteric coated tablets so obtained are finally coated with sugar which may optionally contain colouring matters. The tablets thus obtained are suitable for oral use for therapeutic purposes.

EXAMPLE 4.

A solution is prepared by dissolving 1.5 parts of methyl *p*-hydroxybenzoate, 0.2 part of propyl *p*-hydroxybenzoate and 250 parts sucrose in 1000 parts of water. 150 Parts of N^2 - *iso*propylideneamino - N^1 - *p* - tolylguanidine salicylate and 1.1 parts of purified soya bean lecithin are added and the resulting mixture is then ball-milled for 4 hours. At the end of this time, 5 parts of medium viscosity sodium carboxymethylcellulose and 2.5 parts of a raspberry flavour are added and ball-milling is then continued until the mixture is homogeneous. There is thus obtained an aqueous sweetened suspension suitable for oral use for therapeutic purposes.

EXAMPLE 5.

A mixture of 100 parts of icing sugar, 2 parts of gum tragacanth and 5 parts of N^2-*p*-dimethylaminobenzylideneamino - N^1 - 3 : 4-dimethylphenylguanidine is stirred in a conventional mixer during the addition of a solution of 0.23 part of methyl *p*-hydroxybenzoate, 0.023 part of propyl-*p*-hydroxybenzoate and 0.10 part of a cetyl alcohol polyethylene oxide condensate in 4 parts of ethyl alcohol. Mixing is continued and sufficient 50% by volume of aqueous ethyl alcohol is added to provide a mass suitable for granulation. The mass is granulated in a conventional granulator and after drying at 40—50° C. the dried granules are sieved through a 12 mesh screen. The granules so obtained are charged to a suitable mixer and after the addition of 1 part of a suitable strawberry flavour and mixing for one hour there are obtained dispersible granules suitable for addition to aqueous media to provide formulations suitable for oral administration for therapeutic purposes.

EXAMPLE 6.

A solution of 5 parts of oleic acid, 5 parts of N^2 - *p* - dimethylaminobenzylideneamino-N^1 - phenylguanidine, 0.2 part of propyl-*p*-hydroxybenzoate and 0.04 part of nordihydroguariaretic acid in 230 parts of arachis oil is added with stirring to a solution of 90 parts polyoxyethylene sorbitan mono-oleate and 60 parts of sorbitan mono-oleate in 180 parts of glycerol. A solution of 1 part of methyl-*p*-hydroxybenzoate in 420 parts of water is then added slowly with stirring. The resulting mixture is homogenised by passage through a conventional homogeniser. By the further incorporation of suitable flavouring and sweetening agents there is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

EXAMPLE 7.

20 Parts of coconut oil, 78 parts of arachis oil and 2 parts of beeswax are melted together by heating to 70—80° C. and 0.07 part of propyl gallate is added with stirring. Stirring is continued until solution is complete. 5 Parts of N^1-*p*-acetamidophenyl-N^2-α - methylbutylideneaminoguanidine hydriodide, 40 parts of icing sugar and 0.6 part of saccharin sodium are mixed together in a conventional mixer and the oil solution is added thereto slowly with continual stirring until a homogeneous product is obtained. After the addition of a suitable flavouring agent there is obtained an oily suspension suitable for oral administration for therapeutic purposes.

EXAMPLE 8.

1 Part of N^2-*cyclo*hexylideneamino-N^1-2:4-dimethylphenylguanidine and 1.1 parts of oleic acid are dissolved in 100 parts of arachis oil. The solution is filled into capsules and there is thus obtained soft capsules suitable for oral use for therapeutic purposes.

EXAMPLE 9.

100 Parts of N^2-*p*-N-dimethylaminobenzylideneamino-N^1-3:4-dimethylphenylguanidine are mixed with 100 parts of calcium carbonate. The mixture is filled into hard gelatine capsules and there is thus obtained hard capsules suitable for oral administration for therapeutic purposes.

EXAMPLE 10.

To a stirred mixture of 1 part of N^2-*cyclo*hexylideneamino-N^1-2:4-dimethylphenylguanidine, 0.5 part of cetostearyl alcohol and 20 parts of stearic acid heated to 65—70° C. is added a solution of 8 parts of glycerol and 1.2 parts of triethanolamine in 70 parts of water previously heated to 60° C. The mixture is stirred until cool and then passed through a conventional homogenizer. There is thus obtained a vanishing cream suitable for topical administration for therapeutic purposes.

EXAMPLE 11.

1 Part of N^2-*sec*-butylideneamino-N^1-2:4-dimethylphenylguanidine hydrochloride is pasted with 5 parts of liquid paraffin. The paste is added to 94 parts of white soft paraffin heated at 45—50° C. The mixture is then stirred until cool. There is thus obtained an ointment suitable for topical administration for therapeutic purposes.

EXAMPLE 12.

10 Parts of N^2-*cyclo*hexylideneamino-N^1-2:4-dimethylphenylguanidine are pasted with 50 parts of liquid paraffin. The paste is added to 940 parts of white soft paraffin heated at 45—50° C. The mixture is then stirred until cool. There is thus obtained an ointment suitable for topical administration for therapeutic purposes.

EXAMPLE 13.

1.36 Parts of N^1-*p*-acetamidophenyl-N^2-α-methylbutylideneaminoguanidine hydriodide is dissolved in a solution of 6 parts of glycerol, 0.2 part of a cetyl alcohol-polyethyleneoxide condensate and 0.16 part of methyl *p*-hydroxybenzoate in 100 parts of water. A solution of 0.54 part of sodium salicylate in 2 parts of water is added with stirring and the suspension so obtained is added with stirring to a solution of 6 parts of liquid paraffin, 8 parts of cetostearyl alcohol, 1.8 parts of a cetyl alcoholpolyethyleneoxide condensate, 0.04 part of 2:6-di-tert-butyl-4-methylphenol and 12 parts of arachis oil heated at 60° C. The mixture so obtained is stirred until cool and is then passed through a conventional homogeniser. There is thus obtained a cream suitable for topical administration for therapeutic purposes.

EXAMPLE 14.

To an intimate mixture of 1.25 parts of sterile cetyl trimethylammonium chloride and 25 parts of sterile sodium chloride is added 100 parts of sterile N^1-*p*-chlorophenyl-N^2-pent-2-ylideneaminoguanidine hydrochloride. The mixture is stirred until homogeneous and there is thus obtained a powder suitable for filling into multidose containers which can be used for the extemporaneous preparation of sterile solutions for injection for therapeutic purposes.

EXAMPLE 15.

A solution is prepared by dissolving 1.5 parts of methyl-*p*-hydroxybenzoate, 0.2 part of propyl-*p*-hydroxybenzoate, 8 parts of polyvinyl pyrrolidone and 1.1 part of refined soya bean lecithin in 1000 parts of distilled water. The aqueous vehicle so obtained is sterilised by heating in an autoclave at 10—15 lb. pressure for 30 minutes. 150 Parts of sterile micropulverised N^2-*iso*propylideneamino-N^1-*p*-tolylguanidine salicylate are then added to the cooled aqueous vehicle and the resulting mixture is ball-milled for 15 minutes. There is thus obtained a suspension suitable for parenteral use for therapeutic purposes.

EXAMPLE 16.

0.5 Part of polyoxyethylene sorbitan monooleate and 3.5 parts of soya bean lecithin are dissolved in 300 parts of ether and the solution is filtered through a sterile filter. The filtrate is added to 300 parts of micropulverised sterile N^2-*iso*propylideneamino-N^1-*p*-tolylguanidine salicylate. The mixture is stirred in a conventional mixer until evaporation of the ether is complete. The dry powder is then added gradually to a stirred mixture of 3 parts of sterile sodium carboxymethylcellulose, 0.9 part of methyl *p*-hydroxybenzoate and 0.1 part of propyl *p*-hydroxybenzoate and the resulting mixture is homogenised by further grinding in a micropulveriser. There is thus obtained a dispersible powder suitable for parenteral use for therapeutic purposes.

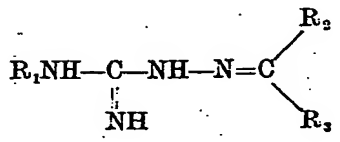
EXAMPLE 17.

A mixture of 2 parts of aluminium stearate and 98 parts of arachis oil is heated slowly with stirring to a temperature of 120° C. The temperature is maintained at this value for 1 hour when gelling is complete and is then raised to 150° C. and maintained thereat for 1 hour. The gel is then cooled and 15 parts of sterile micropulverised N^1-*p*-acetamidophenyl-N^2-α-methylbutylidene-

aminoguanidine hydriodide are incorporated therein with stirring. There is thus obtained a suspension suitable for intramuscular injection for therapeutic purposes.

WHAT WE CLAIM IS:—

1. Pharmaceutical compositions wherein the active ingredient is at least one guanidine compound of the formula:—



wherein R_1 stands for an aryl radical which may optionally be substituted, R_2 stands for hydrogen or for a hydrocarbon radical which may optionally be substituted and R_3 stands for a hydrocarbon radical or for a heterocyclic radical both of which may optionally be substituted, provided that when R_3 stands for a heterocyclic radical R_2 stands for hydrogen, and wherein R_2 and R_3 may be joined, together with the adjacent carbon atom, to form a homocyclic or heterocyclic ring, or a salt thereof.

2. Compositions comprising those salts of the guanidine compounds of the formula given in Claim 1 which are mineral acid salts for example the hydrochlorides and organic acid salts for example the acetates and the salicylates.

3. Compositions as claimed in Claims 1 and 2 which are suitable for oral use for example in the form of tablets, coated or uncoated, aqueous or oily suspensions, dispersible granules, emulsions or hard or soft capsules.

4. Compositions as claimed in Claim 3 wherein the tablets contain the active ingredient in admixture with pharmaceutical excipients for example calcium carbonate or calcium phosphate, granulating and disintegrating agents for example maize starch paste and lubricating agents for example magnesium stearate.

5. Tablet compositions as claimed in Claim 4 wherein for every 100 parts by weight of the composition there is present between about 25 parts by weight and about 95 parts by weight of guanidine compound or a salt thereof and preferably between about 50 parts and about 90 parts by weight of guanidine compound or salt thereof.

6. Compositions as claimed in Claim 3 wherein the aqueous suspensions are formulated from suitable sparingly-soluble salts for example N^2 - *iso*propylideneamino - N^1 - *p*-tolylguanidine salicylate in a sweetened aqueous medium for example aqueous sucrose solution containing a suspending agent and a dispersing agent.

7. Compositions as claimed in Claim 3 wherein the dispersible granules contain the active ingredient admixed with a suspending agent and a dispersing agent.

8. Oily suspensions as claimed in Claim 3 wherein the active ingredient is suspended in a suitable vegetable oil for example arachis oil, sesame oil or coconut oil in the presence of a thickening agent for example beeswax.

9. Emulsions as claimed in Claim 3 which are oil-in-water type emulsions wherein a suitable salt for example the oleate is dissolved in the oil phase in the presence of an emulsifying agent.

10. Emulsions as claimed in Claim 9 wherein the oil phase is arachis oil.

11. Emulsions as claimed in Claims 9 and 10 wherein the emulsifying agent is a naturally-occurring gum for example gum acacia or gum tragacanth, a naturally-occurring phosphatide for example soya bean lecithin, or an ester or partial ester derived from the common fatty acids for example lauric, palmitic, stearic or oleic acid and hexitol anhydrides for example sorbitan mono-oleate and the corresponding condensation products of the said partial esters with ethylene oxide for example polyoxyethylene sorbitan mono-oleate.

12. Hard capsules as claimed in Claim 3 wherein the active ingredient is admixed with an inert solid diluent for example calcium carbonate.

13. Soft capsules as claimed in Claim 3 wherein the active ingredient, in the form of a suitable salt for example the oleate, is dissolved in an oily medium for example arachis oil.

14. Compositions as claimed in Claims 1 and 2 which are suitable for topical use for example in the form of creams, ointments or pastes.

15. Creams as claimed in Claim 14 wherein the active ingredient is in suspension or dissolved in the oil phase.

16. Creams as claimed in Claim 15 wherein the oil phase contains petroleum hydrocarbons for example liquid paraffin, vegetable fats for example arachis oil, long chain aliphatic alcohols for example cetyl alcohol or long chain acids for example stearic acid.

17. Creams as claimed in Claims 15 and 16 wherein for every 100 parts by weight of the composition there is present between 0.1 part and 10 parts by weight, preferably between 1 part and 3 parts by weight, of the guanidine compound or salt thereof.

18. Ointments and pastes as claimed in Claim 14 wherein the active ingredient is dissolved in or dispersed in an anhydrous fatty base for example animal or vegetable fats or a paraffin base.

19. Compositions as claimed in Claims 1 and 2 which are suitable ior fnjection and are in the form of sterile aqueous or oily suspen-

sions and sterile powders for the preparation of aqueous solutions and suspensions.

20. Sterile powders as claimed in Claim 19 wherein a suitable sparingly-soluble salt for example a salicylate is admixed with a suspending agent and a dispersing agent.

21. Sterile aqueous suspensions as claimed in Claim 19 wherein a suitable sparingly-soluble salt for example a salicylate is dispersed in a sterile aqueous medium in the presence of a dispersing agent and a suspending agent.

22. Compositions as claimed in Claims 6, 7, 20 and 21 wherein the suspending agent is sodium carboxymethylcellulose, sodium alginate or polyvinyl pyrrolidone.

23. Compositions as claimed in Claims 6, 7, 20 and 21 wherein the dispersing agent is a naturally-occurring phosphatide for example lecithin or condensation products of ethylene oxide with fatty acids for example polyoxyethylene stearate or fatty alcohols for example heptadeca-ethyleneoxycetanol, or with partial esters derived from the common fatty acids and a hexitol for example polyoxyethylene sorbitol mono-oleate, or with partial esters derived from the common fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan mono-oleate.

24. Oily suspensions as claimed in Claim 19 wherein the active ingredient is dispersed in a suitable oily medium for example a vegetable oil for example arachis oil optionally in the presence of a gelling agent for example aluminium stearate.

25. Sterile powders as claimed in Claim 19 wherein a suitable water-soluble salt for example the hydrochloride is admixed with a bacteriostatic agent for example a long chain quaternary salt for example cetyl trimethylammonium chloride.

26. Compositions, claimed in Claims 1—23, as hereinbefore particularly described and especially with reference to the foregoing examples.

WALTER SCOTT,

Agent for the Applicants.

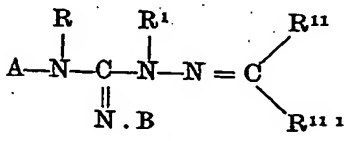
PROVISIONAL SPECIFICATION.

Pharmaceutical Compositions containing Aminoguanidine Derivatives.

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare this invention to be described in the following statement :—

This invention relates to new pharmaceutical compositions and more particularly it relates to new pharmaceutical compositions containing guanidine derivatives.

According to the invention we provide new pharmaceutical compositions wherein the active ingredient is at least one guanidine compound of the formula :—



wherein A, B, R and R^1, which may be the same or different, stand for hydrogen or hydrocarbon radicals, which may optionally bear substituents, R^{11} stands for hydrogen or for a hydrocarbon radical which may optionally be substituted and $R^{11\,1}$ stands for a hydrocarbon radical or for a heterocyclic radical which may optionally be substituted, or a salt thereof.

As suitable salts of the said guanidine compounds there may be mentioned for example mineral acid salts for example the hydrochlorides and organic acid salts for example the acetates.

As suitable compounds of the above stated formula there may be mentioned for example those compounds which are described in our copending Applications Nos. 29837/56, 29838/56 and 29839/56 (Serial Nos. 842,322, 842,323 and 842,324) for example N^1-4-chloro - benzylideneamino - N^2 - methylguanidine, N^1 - 4 - ethoxybenzyldieneamino - N^2 - ethylguanidine, N^1 - 4 - chlorobenzylideneamino - N^2 - *n* - butylguanidine, N^1 - benzylideneamino - N^2 - 4 - chlorophenylguanidine, N^1 - 4 - chlorobenzylideneamino - N^2 - 4^1 - chlorophenylguanidine, N^1 - 4 - chlorophenyl - N^2 - *iso*propylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - *iso*butylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - $1' : 2' : 2'$ - trimethylpropylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - α - methylbenzylideneaminoguanidine, N^1 - 3 : 4 - dichlorophenyl - N^2 - *iso*propylideneaminoguanidine, N^1 - *iso*propylideneamino - N^2 - 4 - hydroxyphenylguanidine, N^1 - benzylideneamino - N^2 - 4 - hydroxyphenylguanidine, N^1 - benzylideneamino - N^2 - 5 - chloro - 2 - methoxyphenylguanidine, N^1 - 5 - chloro - 2 - methoxypehnyl - N^2 - $4'$ - nitrobenzylideneaminoguanidine, N^1-phenyl-N^2 - 4 - methoxybenzylideneaminoguanidine, N^1 - 2 - chlorobenzylideneamino - N^2 - *cyclo* - hexylguanidine, N^1 - *iso*butylideneamino -

N^2 - 4 - ethoxyphenylguanidine, N^1 - 4 - chlorophenyl - N^2 - α - methylbutylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - cinnamylideneaminoguanidine, N^1 - 4 - dimethylaminobenzylideneamino - N^2 - *cyclo*hexylguanidine, N^1 - 4 - dimethylaminobenzylideneamino - N^2 - phenylguanidine, N^1 - benzylideneamino - N^2 - 2 : 4 - dimethylphenylguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 4' - methoxybenzylideneaminoguanidine, N^1 - 4 - dimethylaminobenzylideneamino - N^2 - 2' : 4' - dimethylphenylguanidine, N^1 - 2 - chlorobenzylideneamino - N^2 - 2' : 4' - dimethylphenylguanidine, N^1 - 4 - methylbenzylideneamino - N^2 - 2' : 4' - dimethylphenylguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 3' : 4' - methylenedioxybenzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 4' - nitrobenzylideneaminoguanidine, N^1 - 4 - chlorobenzylideneamino - N^2 - 2' : 4' - dimethylphenylguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 3' - methylbenzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - *iso*propylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - *cyclo*hexylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - α - methylbenzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 2' - methylbenzylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - 2' : 4' - dimethylbenzylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - heptylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - nonylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^1 - methyl - N^2 - methyl - N^2 - *iso*propylideneaminoguanidine, N^1 - 2 : 3 - dimethylphenyl - N^2 - α - methylbutylideneaminoguanidine, N^1 - 4 - chlorophenyl - N^2 - *cyclo*hexylideneaminoguanidine, N^1 - 2 : 4 - dichlorophenyl - N^2 - *sec* - butylideneaminoguanidine, N^1 - 2 : 4 - dichlorophenyl - N^2 - α - methylbutylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - *iso*butylideneaminoguanidine, N^1 - 2 : 4 - dimethylphenyl - N^2 - α - methylbutylideneaminoguanidine and the known compound, N^1-benzylideneamino-N^2-phenylguanidine.

The said pharmaceutical compositions may be in the form of tablets wherein the active ingredient is admixed with pharmaceutical exipients known to be suitable in the manufacture of such tablets. Suitable pharmaceutical excipients may be for example inert diluents for example calcium carbonate, granulating agents for example maize-starch paste and lubricating agents for example magnesium stearate. The said tablets may be uncoated or they may be coated to withstand disintegration in the presence of gastric juice.

The said tablet compositions may be formulated so that for every 100 parts by weight of the composition there is present between about 25 parts by weight and about 75 parts by weight of the appropriate guanidine compound or a salt thereof for example about 50 parts by weight of the said guanidine compound or a salt thereof.

The pharmaceutical compositions may furthermore be in the form of creams, ointments or pastes wherein the active ingredient is admixed with pharmaceutical excipients known to be suitable in the manufacture of such creams, ointments or pastes. The said creams may be in the form of oil-in-water or water-in-oil type of emulsions dependent upon the choice of suitable excipients and emulsifying agents. Suitable pharmaceutical excipients may be for example suitable mixtures of oily or fatty bases for example petroleum hydrocarbons for example liquid paraffin, vegetable fats for example arachis oil, long chain aliphatic alcohols for example cetyl alcohol, emulsifying agents for example condensation products of ethylene oxide with long chain aliphatic alcohols for example heptadeca-ethyleneoxycetanol and humectants for example polyhydric alcohols for example glycerol. Such cream compositions may be formulated so that for every 100 parts by weight of the composition there is present between about 0.1 part by weight and about 10 parts by weight of the appropriate guanidine compound or a salt thereof for example about 2 parts by weight of the said guanidine compound or a salt thereof. The said ointments or pastes are such that the active ingredient or ingredients may be dissolved in or dispersed in an aqueous phase or an anhydrous fatty base for example animal or vegetable fats or a paraffin base. The creams, ointments or pastes may also optionally contain a suitable preservative and/or a suitable anti-oxidant.

The pharmaceutical compositions may also be in the form of sterile aqueous solutions thereof and such solutions may contain known excipients for example a preservative for example chlorocresol, and agents suitable for the provision of an isotonic solution for example boric acid and sodium chloride. The said aqueous solutions may be formulated so that for every 100 parts by weight of the compositions there is present between about 1 part by weight and about 10 parts by weight of the appropriate guanidine compound or a salt thereof for example about 5 parts by weight of the said guanidine compound or a salt thereof.

The pharmaceutical compositions may also be in the form of syrups or emulsions suitable for oral use. The said syrups may contain the active ingredient dissolved in an aqueous glycerol medium which may optionally contain colouring matter, a flavouring agent and a demulcent. The oral emulsions may be of the oil-in-water or water-in-oil type emulsions wherein the emulsifying agents may be esters or partial esters derived from the common fatty acids for example lauric, palmitic, stearic and oleic acid and hexitol

anhydrides for example hexitans and hexides derived from sorbitol for example sorbitan mono-oleate and the corresponding condensation products of the said partial esters with ethylene oxide for example polyoxyethylene sorbitan mono-oleate. A suitable oily base may be for example a vegetable base for example olive oil.

The pharmaceutical compositions may also be in the form of lotions suitable for topical application and such lotions may be formulated in an aqueous glycerol base containing suitable excipients for example calamine and/or zinc oxide.

The pharmaceutical compositions of this invention possess valuable therapeutic properties and they are particularly useful in the treatment of allergic and inflammatory conditions.

The invention is illustrated but not limited by the following examples in which the parts are by weight :—

EXAMPLE 1.

A mixture of 100 parts N^1-benzylideneamino-N^2-*p*-chlorophenylguanidine hydrochloride and 100 parts of calcium carbonate is granulated by admixture with a sufficient quantity of 10% maize-starch paste. The granules are passed through a 16-mesh screen and are then dried at 50—55° C. After further passages through a 16-mesh screen 1 part of magnesium stearate is added to the granules and the mixture is compressed. There are thus obtained tablets suitable for oral administration for therapeutic purposes.

EXAMPLE 2.

To a mixture of 6 parts of liquid paraffin, 12 parts of arachis oil, 8 parts of cetyl alcohol and 1.8 parts of heptadeca-ethyleneoxycetanol heated to 60° C. is added with stirring a mixture of 6 parts of glycerol, 0.2 part of heptadeca-ethyleneoxycetanol and 2.7 parts of N^1-*iso*propylideneamino-N^2-2,4-dimethylphenylguanidine hydrochloride in 102 parts of water at 60° C. Stirring is continued until a cream is formed and the temperature falls to 40° C. The mixture is then homogenised by passage through a colloid mill and there is obtained a cream suitable for topical application for therapeutic purposes.

EXAMPLE 3.

5 parts of N^1-*iso*propylideneamino-N^2-*p*-chlorophenylguanidine hydrochloride are dissolved in 100 parts of distilled water containing 0.2 part of chlorocresol and the solution is autoclaved at a pressure of 10—15 lb. per square inch during 30 minutes. There is thus obtained a sterile aqueous solution suitable for parenteral administration for therapeutic purposes.

EXAMPLE 4.

0.2 part of methyl *p*-hydroxybenzoate, 0.1 part of propyl *p*-hydroxybenzoate and 0.02 part of saccharin are dissolved in a mixture of 60 parts of glycerol and 140 parts of water. 5 parts of N^1-*cyclo*hexylideneamino-N^2-2 : 4-dimethylphenylaminoguanidine hydrochloride are then dissolved in the resultant solution and there is thus obtained a syrup suitable for oral administration for therapeutic purposes.

EXAMPLE 5.

To a mixture of 1 part of polyoxyethylene sorbitan mono-oleate, 1.5 parts sorbitan mono-oleate and 12.5 parts of olive oil in which is dissolved 0.5 part N^1-α-methylbutylideneamino - N^2 - *p* - chlorophenylguanidine, are added with stirring 10 parts of water. The emulsion so formed is homogenised by passage through a conventional homogeniser. By the incorporation of a suitable preservative and anti-oxidant there is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

EXAMPLE 6.

To a solution of 2.5 parts N^1-*p*-dimethylaminobenzylideneamino - N^2 - phenylaminoguanidine hydrochloride in a mixture of 10 parts of glycerol and 250 parts of water is added a mixture of 20 parts of calamine and 13 parts of zinc oxide. There is thus obtained a lotion suitable for topical application for therapeutic purposes.

WALTER SCOTT,
Agent for the Applicants.

Abingdon : Printed for Her Majesty's Stationery Office, by Burgess & Son (Abingdon), Ltd.—1960.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2,
from which copies may be obtained.